In re Application of PATENT Rosenmund et al. ATTORNEY DOCKET NO.: VOSS1160

Application No.: 09/807,499 Filed: November 5, 2001

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# **Amendments to the Specification:**

Please delete the paragraph at page 1, lines 2-24.

Please replace the paragraph beginning at page 1, line 25, with the following amended paragraph:

## BACKGROUND OF THE INVENTION

Several documents are cited throughout the text of this specification. Each of the documents cited herein (including any manufacturer's specifications, instructions, etc.) are hereby incorporated by reference; however, there is no admission that any document cited is indeed prior art for patentability of the present invention.

Please insert the following paragraphs at page 6, prior to line 28:

### SUMMARY OF THE INVENTION

The present invention relates to a nucleic acid molecule encoding a (poly)peptide which has an amino acid sequence of a glutamate receptor of the AMPA-type and functions as a non-desensitizing AMPA-receptor or as a non-desensitizing subunit thereof, wherein the leucine corresponding to position 497 of the wildtype rat AMPA-receptor GluR1<sub>flip</sub> or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of the wildtype rat AMPA-receptor GluR1<sub>flip</sub> is replaced by an aromatic amino acid. The invention further relates to (poly)peptides encoded by said nucleic acid molecules, vectors and hosts comprising said nucleic acid molecules, as well as to methods for producing (poly)peptides encoded by said nucleic acid molecules. The present invention also provides for antibodies specifically directed to (poly)peptides encoded by said nucleic acid molecules. Additionally, the invention relates to a method for the blocking of desensitization of a glutamate receptor of the AMPA-type, comprising the step of replacing a leucine which corresponds by comparison of homology to position 497 of the rat AMPA-receptor GluR1 by an aromatic amino acid and methods for identifying and/or characterizing molecules which are capable of interaction with glutamate receptors of the AMPA type. The invention also relates to

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the one of the aforementioned nucleic acid molecules, (poly)peptides, hosts, vectors and/or antibodies as biosensors, for the characterization of glutamate receptor channel properties and/or for the preparation of pharmaceutical compositions. Furthermore, the invention provides for pharmaceutical compositions, diagnostics and kits comprising and/or employing the compounds of the invention.

### BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1D are graphical representations showing the desensitization properties of GluR1 receptors.

Figures 2A-2F are graphical representations showing the role of the N-terminal region of AMPA-type glutamate receptor desensitization.

Figures 3A-3B are graphical representations showing the desensitization properties of GluR3-'S1' chimeras.

Figures 4A-4E are graphical representations showing that the mutations of T504A, L507Y and E511K on GluR3<sub>flip</sub> differentially control desensitization and agonist binding.

Figures 5A-5D are graphical representations showing the specificity of L507 for AMPA receptor desensitization.

Figures 6A-6D are graphical representations showing that the aromatic residues in position 507 remove desensitization.

Figures 7A-7B are graphical representations showing that Kainate elicits fast desensitizing. responses at AMPA receptors.

Figure 8 shows the alignment of partial amino acid sequences of different AMPA receptors (subunits) from rat, human and mouse. Shown are residues 460-519 of SEQ ID NO: 1 (rat GluR1); residues 467-526 of SEQ ID NO: 2 (rat GluR2); residues 470-529 of SEQ ID NO: 3 (rat GluR3); residues 468-528 of SEQ ID NO: 4 (rat GluR4); residues 460-519 of SEQ ID NO: 5

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(human GluR1); residues 467-526 of SEQ ID NO: 6 (human GluR2); residues 476-535 of SEQ

ID NO: 7 (human GluR3); residues 468-528 of SEQ ID NO: 8 (human GluR4); residues 460-519

if SEQ ID NO: 9 (mouse GluR1); and residues 467-526 of SEQ ID NO: 10 (mouse GluR2).

Please replace the paragraph beginning at page 6, line 28, with the following amended paragraph:

#### **DETAILED DESCRIPTION**

Accordingly, the present invention relates to a nucleic acid molecule encoding a (poly) peptide which has an amino acid sequence of a glutamate receptor of the AMPA-type and/or of a subunit of said receptor and functions as a non- desensitizing AMPA-receptor or as a non-desensitizing subunit thereof, wherein the leucine corresponding to position 497 of the wildtype rat AMPA-receptor GluRl<sub>flip</sub> or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of the wildtype rat AMPA-receptor GluRl<sub>flip</sub> is replaced by an aromatic amino acid.

After page 57, please insert the following paragraph:

#### **ABSTRACT**

The present invention relates to a (poly)peptide which has an amino acid sequence of a glutamate receptor of the AMPA-type and functions as a non-desensitizing AMPA-receptor or as a non-desensitizing subunit thereof, wherein the leucine corresponding to position 497 of the wildtype rat AMPA-receptor GluR1<sub>flip</sub> or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of the wildtype rat AMPA-receptor GluR1<sub>flip</sub> is replaced by an aromatic amino acid. Also provided are nucleic acid molecules encoding the polypeptide.